Impact of Implementing a "FIB-4 First" Strategy on a Pathway for Patients With NAFLD Referred From Primary Care

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Detection of advanced fibrosis in nonalcoholic fatty liver disease (NAFLD) is essential for stratifying patients according to the risk of liver-related morbidity. Noninvasive methods such as vibration-controlled transient elastography (VCTE) and Fibrosis-4 index (FIB-4) have been recommended to identify patients for further assessment. The aim of this study was to assess the potential impact of implementing a "FIB-4 First" strategy to triage patients entering a NAFLD assessment pathway. The pathway for patients with suspected NAFLD was piloted at a tertiary liver center. Referral criteria were 16-65 years old, elevated alanine aminotransferase and/or steatosis on imaging, and absence of a previous liver diagnosis. A registered nurse risk-stratified all patients based on VCTE and FIB-4 was calculated. Potential alternative diagnoses were excluded with bloodwork. A total of 565 patients underwent risk stratification with VCTE with a 97% success rate. Ten percent had VCTE of at least 8 kPa; 560 patients had FIB-4 available for analysis and 87% had values less than 1.3. Of those with a FIB-4 of at least 1.3, 69% had a VCTE less than 8 kPa. Further modeling showed that the presence of diabetes, age, and body mass index had only a moderate impact on the association between FIB-4 and elastography values if using a FIB-4 threshold of 1.3. *Conclusion:* **A FIB-4 threshold of 1.3 was acceptable for excluding the presence of advanced fibrosis (assessed by VCTE). A staged risk-stratification model using FIB-4 and VCTE could save up to 87% of further assessments. This model could improve accessibility by moving the initial fibrosis evaluation to the medical home and helping to prioritize patients for further specialized care. (*Hepatology Communications* 2019;3:1322-1333).**

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In patients with nonalcoholic fatty liver disease (NAFLD), the estimation of liver fibrosis is essential for risk stratification and prediction of liver-related complications.[1,2] Of the existing tests that are in common use, liver enzymes are unreliable predictors of fibrosis. Imaging is limited by the detection of fibrosis at advanced stages,[3] leading to late presentation with cirrhosis or hepatocellular carcinoma.[4] Liver biopsy, considered the gold standard for disease staging, has limited utility in the coming NAFLD epidemic, as it is costly and carries inherent risk.[5] In more recent years, noninvasive liver elastography such as vibration-controlled transient elastography (VCTE) and shear-wave elastography have gained favor as more feasible and effective options

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CI, confidence interval; FIB-4, Fibrosis-4 index; IQR, interquartile range; NAFLD, nonalcoholic fatty liver disease; PCP, primary care provider; RN, registered nurse; VCTE, vibration-controlled transient elastography.

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for the detection of fibrosis in NAFLD.[6] With the rising rates of NAFLD, limited access to elastography, and cost considerations, it is clear that the reliance on noninvasive liver elastography as the primary modality of risk stratification is not a tenable model. Additionally, in settings where there is wide geographical population distribution, patients must travel long distances to reach centers where fibrosis assessment is offered. Given the increasing prevalence of NAFLD, it is imperative that alternative models for identifying patients at risk of progressive disease are developed.[7,8] This will allow for early risk stratification and management, appropriate referral to hepatology for more advanced cases, and improved access for other patients awaiting hepatology consultation.

The Fibrosis 4 index (FIB-4) is a score based on readily available blood tests that are routinely measured (age, aspartate aminotransferase [AST], alanine aminotransferase [ALT], and platelet count). FIB-4 has shown a high discriminative ability (area under the receiver operating characteristic curve = 0.86) for advanced fibrosis. Using a decision threshold of 1.3, FIB-4 has demonstrated reliability at excluding advanced fibrosis in NAFLD.[9-11] FIB-4 has been suggested as a prescreening strategy to improve the efficiency of referral for specialized liver care,[12,13] prioritizing patients who are at higher risk of significant liver disease. This type of staged testing has been recommended in other areas where the pretest probability is low, such as ischemia detection in low-risk patients with coronary artery disease[14] and screening for colorectal cancer in low-risk individuals.[15]

As part of a quality improvement initiative of using VCTE for risk stratification, we piloted a referral pathway to assess fibrosis in patients with suspected NAFLD. We retrospectively analyzed prospectively collected data from the pilot clinic and modeled the potential impact of implementing a FIB-4 First strategy to pre-triage patients entering the pathway, as opposed to offering VCTE to all referred patients.

Methods

PATIENTS

A referral pathway for patients with suspected NAFLD was piloted at a tertiary care center in Edmonton, Canada, from November 2016 to October 2018 (Fig. 1). Primary care providers (PCPs) were engaged through one of eight primary care networks and received a short educational update on NAFLD and the importance of fibrosis assessment. Physicians were briefed about the registered nurse (RN) pilot clinic and referral process for patients with suspected NAFLD. The combined estimated population of the participating networks was 850,000 adults. Patients with suspected NAFLD were referred from PCPs to the Division of Gastroenterology at the University of Alberta Hospital. The referral criteria for the clinic were elevated ALT and/or steatosis on imaging, and age of 16-65 years. PCPs were not required to rule out co-existing causes of chronic liver disease. Patients who were found to have a chronic liver disease after review by the RN were booked with a hepatologist and were not included in the analysis. Women who regularly drank more than 3 drinks on any single day or 7 drinks per week and men who regularly drank

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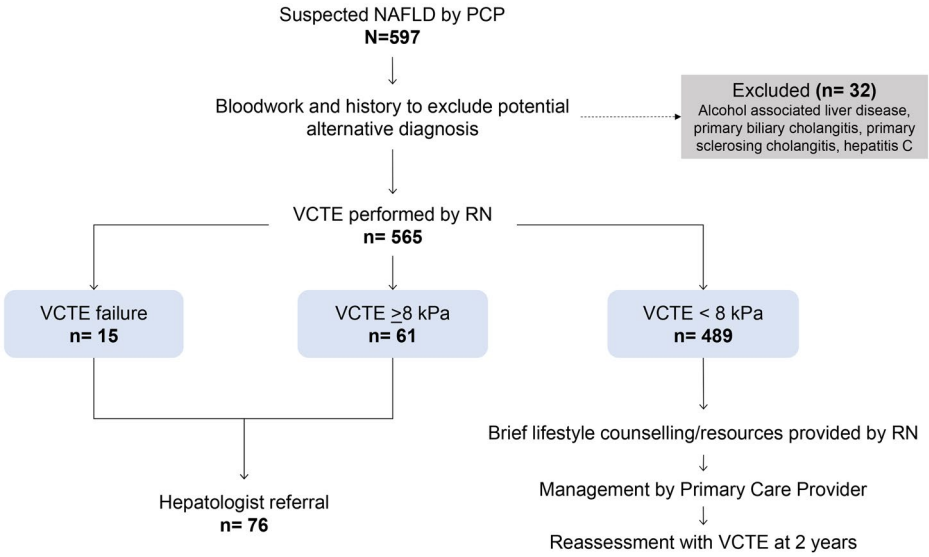

FIG. 1. VCTE-based referral pathway for NAFLD used in the pilot clinic.

more than 4 drinks on any single day or 14 drinks per week on referral were classified as heavy drinkers and not included in the NAFLD pathway analysis.[16] Patients who were found to have significant alcohol use by the RN and who were not reported by the PCP were included in the analysis, as these patients would not have been identified in the FIB-4 pathway as alcoholic fatty liver.

CLINICAL, LABORATORY, AND VCTE ASSESSMENTS

Patients completed bloodwork according to the American College of Gastroenterology to rule out alternative liver diagnoses.[17] Patients were then seen by an RN, who reviewed their medical histories and completed fibrosis and steatosis assessment with VCTE. All VCTE tests were completed by a single operator using a Fibroscan 502 touch (M Probe, XL Probe; KNS Inc., Scarborough, Canada). A triage diagnosis of NAFLD was defined as a controlled attenuation parameter reading of 250 dB/m or higher, with no other liver disease etiology identified. Patients were considered to have concerning fibrosis if the VCTE reading was 8 kPa or higher. This threshold was determined using conservative estimates based on published literature.[6,8,18] Patients were triaged to see the hepatologist if there was concern for fibrosis or if a valid VCTE was not obtained. VCTE failures (no measurement obtained or unreliable results) were defined as fewer than 10 valid shots or interquartile range (IQR)/median value greater than 30% with a VCTE median of 7.1 kPa or higher.[19] Patients with a VCTE less than 8 kPa (low risk for advanced fibrosis) were counseled by the RN to make lifestyle changes and were scheduled for re-assessment with VCTE in 2 years. These patients were discharged to the care of their PCP with recommendations based on the American Association for the Study of Liver Diseases practice guidance for NAFLD.

Approval was received from the University of Alberta Research Ethics Board. Data were extracted from the electronic medical record, anonymized, and prospectively entered into a database for subsequent analysis.

MODELING THE IMPACT OF A FIB-4 FIRST STRATEGY FOR TRIAGING PATIENTS AT RISK OF LIVER-RELATED MORBIDITY

We retrospectively assessed the potential impact of implementing a FIB-4-based triage system to the pilot clinic population, using a decision threshold of 1.3. Patients with a FIB-4 of less than 1.3 would be classified as low risk and would remain under the care of their PCP with no further liver assessment. Re-assessment with FIB-4 would be recommended in

2 years. Patients with a FIB-4 of 1.3 or higher would be further assessed with VCTE, and those with values of 8 kPa or higher or indeterminate results would be referred to a hepatologist (Fig. 2). The number of VCTE assessments and specialist visits that would be saved by this strategy were key readouts. Because age and body mass index (BMI) have been described to influence FIB-4 prediction of fibrosis,[20,21] and the presence of diabetes significantly increases the risk of advanced fibrosis, we further assessed the impact of these three variables on FIB-4-based predictions (as detailed subsequently).

STATISTICAL ANALYSIS

Numerical variables were described as the median (IQR), and categorical variables as absolute and relative frequencies. Nonparametric local regression (locally weighted least squares or *loess*) was used to graphically explore the associations between FIB-4 and VCTE.[22] The association between FIB-4 and VCTE of 8 kPa or higher was modeled with logistic regression. The final model was corrected for optimism with bootstrapping (200 resamplings) and presented as a nomogram. The association among FIB-4, glucose metabolism status (classified as normal, prediabetes, and diabetes [Table 1]), age, and BMI was explored with linear regression (detailed methods are provided in the Supporting Information). Confidence intervals (CIs) for proportions were calculated using the Clopper–Pearson method. Analysis was conducted within R statistical software (R Foundation for Statistical Computing, Vienna, Austria) using the *rms* (https://CRAN.R-project.org/package=rms), *ggplot2* (H. Wickham, Elegant Graphics for Data Analysis, Springer-Verlag New York, 2016), and *ggridges* (https://CRAN.R-project.org/package=ggridges) packages.

Results

CHARACTERISTICS OF THE STUDY POPULATION

At the time of analysis, 565 patients had entered the pilot referral pathway. Baseline characteristics of the patients are presented in Table 1. The XL probe was used in 57% of readings and there were 15 (2.7%) VCTE failures. Assessment by a hepatologist was triggered by 13% of patients after risk stratification with VCTE, 10.3% for VCTE of 8 or higher, and 2.7% for VCTE failure.

MODELING THE RELATIONSHIP BETWEEN FIB-4 AND VCTE

Figure 3A,B shows the observed association between FIB-4 values and the probability of finding a VCTE of 8 kPa or higher, while Fig. 3C,D shows the distribution of the FIB-4 values in our sample. A FIB-4 value of 1.3 accurately reflected a change in risk of finding a VCTE at 8 kPa or higher. We then modeled the association between FIB-4 and the probability of a VCTE of 8 kPa or higher with logistic

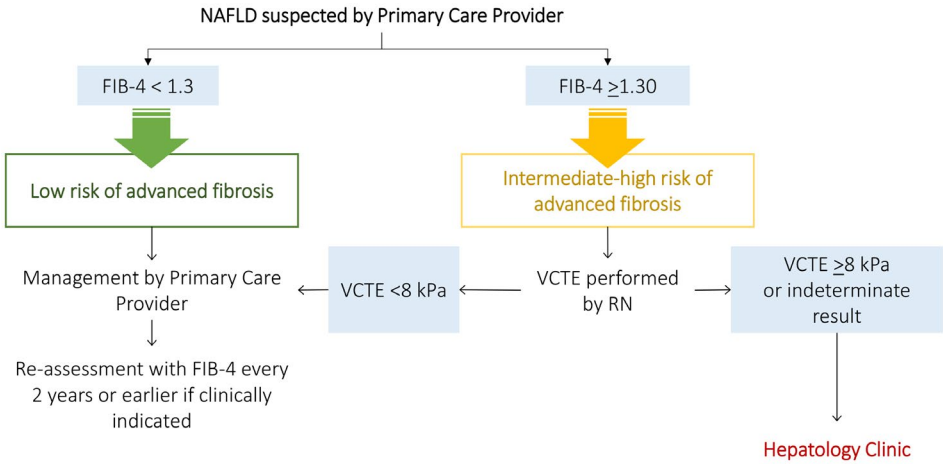

FIG. 2. Theoretical implementation of the two-stage risk stratification model sequentially using FIB-4 and VCTE.

TABLE 1. BASELINE CHARACTERISTICS OF PATIENTS RISK-STRATIFIED WITH VCTE

Variable	n = 565 Median (IQR)/n (%)
Age	41 (32-48)
Sex, n (% males)	72%
Reason for referral, n (%)	
Elevated liver enzymes	164 (29.0%)
Fatty liver on ultrasound	100 (17.7%)
Elevated enzymes *and* fatty liver on ultrasound	301 (53.3%)
BMI, kg/m^2	31 (28-35)
AST, U/L	36 (28-48)
ALT, U/L	63 (44-89)
Total bilirubin, umol/L	11 (9-15)
Albumin, g/L	45 (44-47)
Plt, 10^9/L	240 (204-282)
HbA1C, %	5.6 (5.3-6)
Diagnosis, n (%)	
NAFLD	504 (89.2%)
ALD	39 (6.9%)
Normal ALT/mild fat	17 (3.0%)
Abnormal ALT/mild fat	5 (0.9%)
Components of the metabolic syndrome,* n (%)	
Obesity†	
BMI < 25 kg/m^2	48 (8.5%)
BMI 25-30 kg/m^2	193 (34.2%)
BMI > 30 kg/m^2	324 (57.3%)
Fasting plasma glucose‡	
Normal (FPG ≤ 5.6 and A1C < 5.7)	238 (42.1%)
Prediabetes (FPG 5.6-6.9 mmol/L or A1C 5.7%-6.4%)	227 (40.2%)
Diabetes (on receipt, FPG ≥ 7.0 mmol/L or A1C ≥ 6.5%)	100 (17.7%)
Serum triglyceride ≥ 1.7 mmol/L	290 (51.3%)
Low HDL (<1.0 mmol/L [men], <1.3 mmol/L [Women])	54 (9.6%)
Hypertension (previously diagnosed)	140 (24.8%)
FIB-4 index	0.75 (0.58-10.5)
Use of XL probe, n (%)	321 (57%)
VCTE failure	15 (2.7%)
Technical failures	4 (0.7%)
Unreliable readings	11 (2%)
VCTE, kPa	5.3 (4.4-6.7)
CAP, dB/m	327 (287-362)
VCTE ≥ 8 kPa (%)	61 (10.3%)

*According to the International Diabetes Federation definition of the Metabolic Syndrome (https://www.idf.org/our-activities/advocacy-awareness/resources-and-tools/60:idfconsensus-worldwide-definitionof-the-metabolic-syndrome.html).
†Abdominal circumference was not measured in the pilot clinic; BMI was used as a proxy for central adiposity.
‡According to the American Diabetes Association Standards of Medical Care in Diabetes 2019 (https://doi.org/10.2337/dc19-Srev01).
Abbreviations: ALD, alcoholic liver disease; CAP, controlled attenuation parameter; FPG, fasting plasma glucose; HbA1C, hemoglobin A1C; HDL, high-density lipoprotein; and PLT, platelet count.

regression (Supporting Fig. S1). The nomogram in Fig. 3D shows the modeled probability of finding a VCTE of 8 kPa or higher according to FIB-4 values. A FIB-4 of 1.3 predicted a 12.5% (95% CI 10-16) probability of a VCTE of 8 kPa or higher. Furthermore, Fig. 3C,D shows that in our sample, FIB-4 showed a

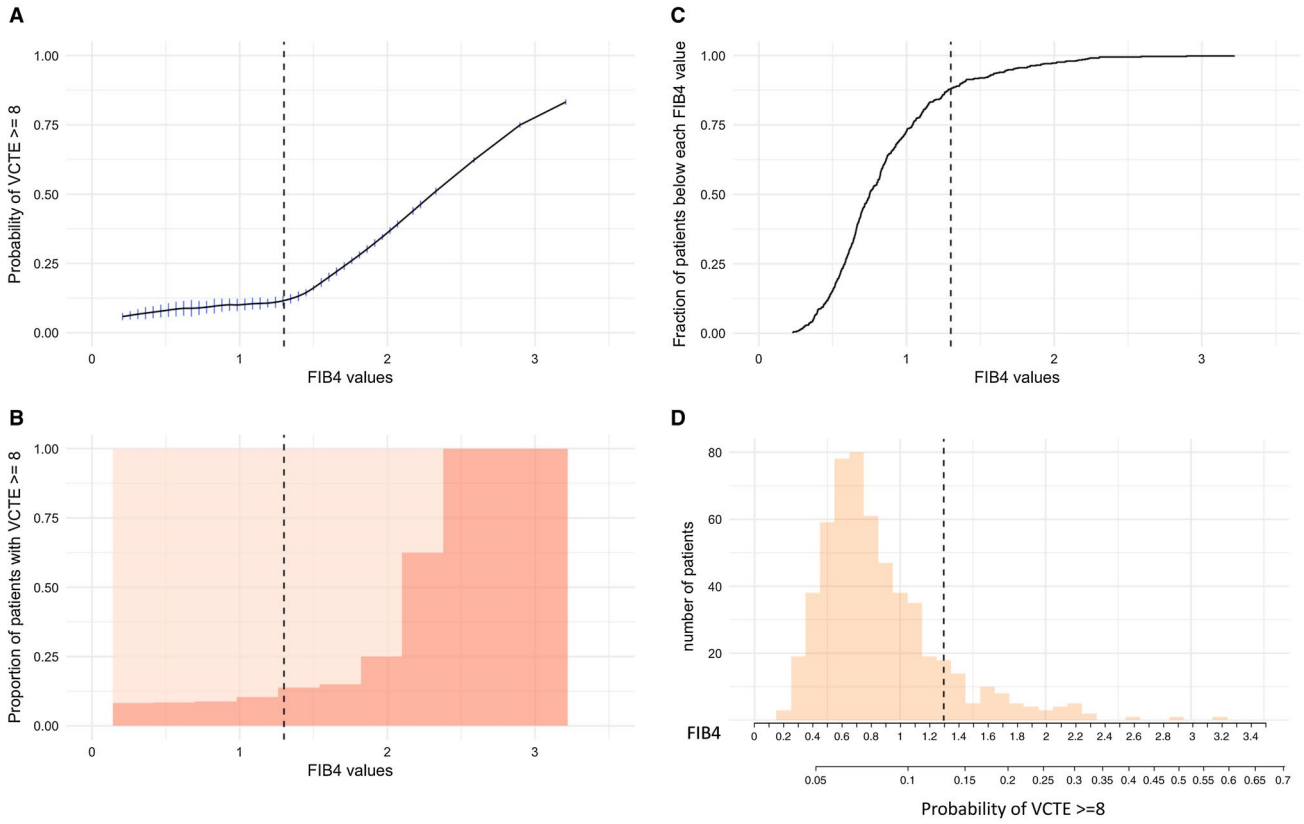

FIG. 3. Sample distribution of FIB-4 values and association between FIB-4 and the risk of finding a VCTE greater than 8 kPa. (A) Probability of VCTE greater than 8 according to FIB-4. A FIB-4 value greater than 1.3 (dashed line) is associated with a significant change in the risk of finding a VCTE of 8 kPa or higher (curve constructed with nonparametric local regression, as reported in statistical methods with vertical lines showing the density of the data at each FIB-4 value). (B) Proportion of patients (in dark orange) with VCTE greater than 8 kPa according to FIB-4 values. (C) Cumulative distribution function of FIB-4 values. The line represents the fraction of patients with values below each FIB-4 value. (D) Nomogram showing the modeled probability of finding a VCTE greater than 8 kPa according to FIB-4 values, with a histogram showing the distribution of the observed FIB-4 values. A FIB-4 value of 1.3 was associated with a probability of 12.5% of finding a VCTE greater than 8 kPa.

skewed distribution with most patients having FIB-4 values less than 1.3.

EFFECTS OF DIABETES, OBESITY, AND AGE ON FIB-4 PREDICTIONS

We next tested whether the presence of prediabetes, diabetes, or obesity influenced FIB-4 prediction of fibrosis (as assessed by VCTE), and if this could have a significant impact on the use of 1.3 as the threshold for defining low risk. As shown in Fig. 4A, the proportion of patients with FIB-4 of at least 1.3 was progressively higher in patients with normal glucose metabolism (8%), prediabetes (15%), and diabetes (31%). In addition, patients with diabetes and low FIB-4 (<1.3) had a higher probability of having a VCTE of 8 kPa or higher than patients with prediabetes or normal glucose metabolism (Fig. 4B), but this difference was progressively blunted when predicting VCTE values of 10 kPa or 12 kPa (thresholds that have also been proposed for advanced fibrosis and cirrhosis,[23,24] respectively [Fig. 4B-D]). Interestingly, as shown in Fig. 4B-D, lowering the threshold of FIB-4 would not have resulted in the identification of patients at lower risk of fibrosis.

Patients with and without obesity had FIB-4 values of at least 1.3 in 14% and 11% of the cases (Supporting Fig. S2A). Obese patients with low FIB-4 had a slightly higher probability of having a VCTE of at least 8, 10, and 12 kPa than patients without obesity

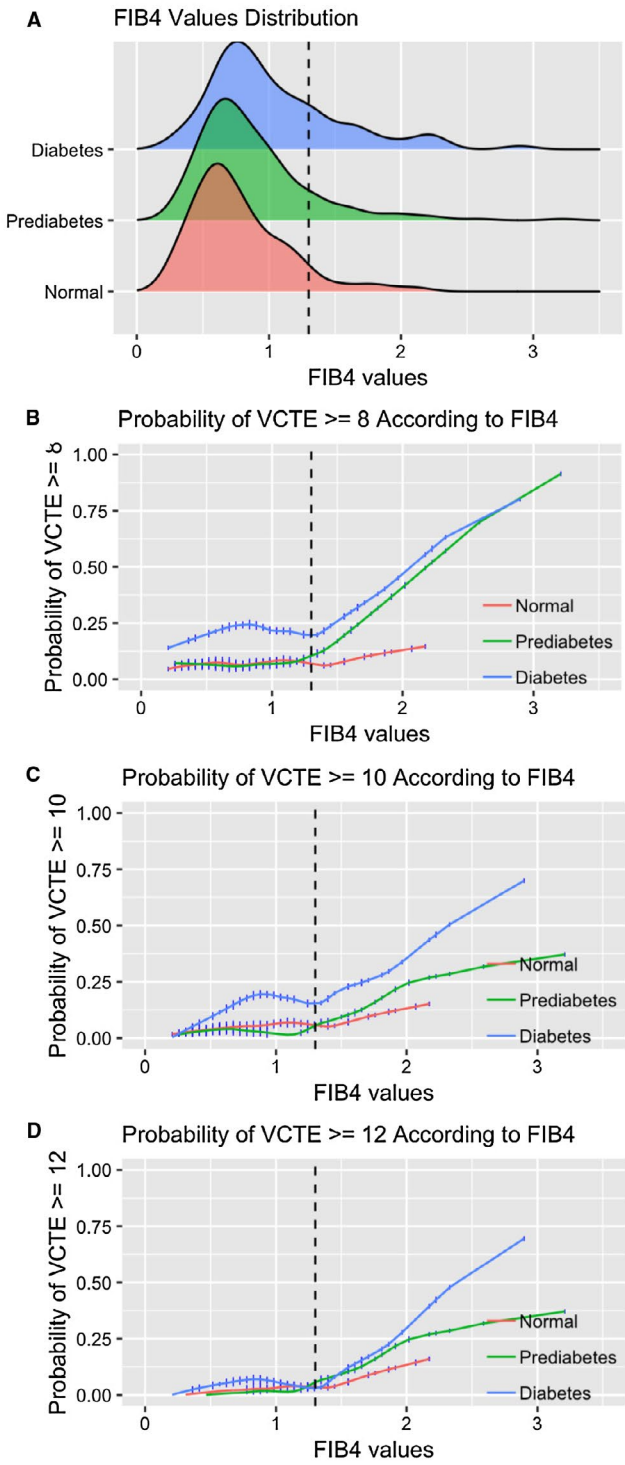

FIG. 4. Impact of the presence of prediabetes and diabetes on FIB-4-based predictions. (A) Patients with prediabetes and diabetes had a higher proportion of patients with FIB-4 values above the 1.3 threshold (dashed line). (B-D) Probability of finding VCTE values greater than 8, 10, and 12 kPa according to FIB-4 values, for patients without abnormalities in glucose metabolism, prediabetes, and diabetes. Curves were constructed with nonparametric local regression, with vertical lines showing the density of the data at each FIB-4 value.

(Supporting Fig. S2B-D). As with diabetes, using a lower FIB-4 threshold in obese patients would not have resulted in the identification of patients at lower risk of fibrosis.

To further assess the influence of prediabetes/diabetes, BMI, and age on the FIB-4 predictions of VCTE, we conducted a linear regression analysis that showed how all four variables were associated with VCTE values (Supporting Information). Age showed a significant interaction with FIB-4 in VCTE prediction. As a result, at low FIB-4 values, increased age was associated with lower predicted values of VCTE, whereas at high FIB-4 values, increased age was associated with higher predicted VCTE values. Figure 5 shows the predicted mean VCTE values based on FIB-4 as modified by age, BMI, and presence of prediabetes/diabetes.

EFFECTS OF IMPLEMENTING A FIB-4 FIRST STRATEGY IN OUR PILOT PROGRAM ON THE NEED FOR VCTE AND SPECIALIST ASSESSMENT

At the time of assessment with VCTE, 560 patients had an available FIB-4 index (Fig. 6) (5 patients from the original pilot clinic had missing AST [n = 4] or platelet values [n = 1]). Eighty-seven percent of the patients (95% CI: 84-90) were stratified as low-risk by FIB-4 (FIB-4 < 1.3). Of the patients who were stratified as low-risk, 41 of 489 patients (8%) had a VCTE reading of 8 kPa or higher (with 14 of 489 [3%] and 10 of 489 [2%] having VCTE readings over 10 and 12, respectively). Characteristics of this discordant group can be found in Supporting Table S1. Of these, 21 patients had a repeat VCTE by a hepatologist, of whom 15 had values less than 8 kPa. Only 8 patients (with a median VCTE of 11.9) proceeded to a liver biopsy, with 3 showing advanced fibrosis.

In patients stratified to the high-risk category (FIB-4 > 1.3), 69% had a VCTE of less than 8 kPa, 4% were technical failures, and 27% had a VCTE of 8 kPa or higher. Therefore, using a two-step strategy, in which only patients with a FIB-4 of 1.3 or higher and a VCTE of 8 kPa or higher were sent for further evaluation, only 22 of 560 patients (4%; 95% CI 2%-6%) would have ended up in a hepatology clinic.

EFFECT OF AGE ON THE NUMBER OF PATIENTS TRIAGED AS LOW-RISK

In the pilot clinic, referral criteria stipulated a maximum age of 65. This resulted in a relatively low mean age in our sample (40 years old). Because age is a component of FIB-4, this might have resulted in an overestimation of the patients who would be triaged as low-risk with a FIB-4 strategy.

To assess the potential impact of implementing such a program in patients of more advanced age, we modeled the number of patients triaged by FIB-4 in two ways. First, we added 5 or 10 years of age to all patients (which would increase the mean age to 45 and 50 years old, respectively). Second, we selected only those patients with age greater than 43 (which resulted in a mean age of the sample of 51 years old). Table 2 provides the results of this sensitivity analysis, showing that the predicted number of patients triaged as low-risk by FIB-4 if the mean age of the population was 10 years older than in our sample would be approximately 75%.

Discussion

In this study we show that a large proportion of patients with suspected NAFLD referred for assessment can be safely triaged using a "FIB-4 First" strategy. With a FIB-4 threshold of 1.3, less than 15% of the patients in our program would have been referred for further assessment. Only 4% of patients would have required a review by a hepatologist after subsequent risk stratification with VCTE.

Previous data validating FIB-4 as a predictor of fibrosis in patients with NAFLD showed a substantially lower number of patients classified as low-risk. Indeed, in the study published by McPherson et al., only 62% of the sample had a FIB-4 of less than 1.3.[9] Several potential explanations might account for this difference. In this same study, all patients had a liver biopsy, which may have biased the study sample toward a higher proportion of patients with more severe disease, as are often seen in a tertiary center. In contrast, our sample reflected a cohort of unselected patients referred by PCPs and were likely to have earlier disease. The lower mean FIB-4 in our population (0.87) compared with the one of the McPherson study

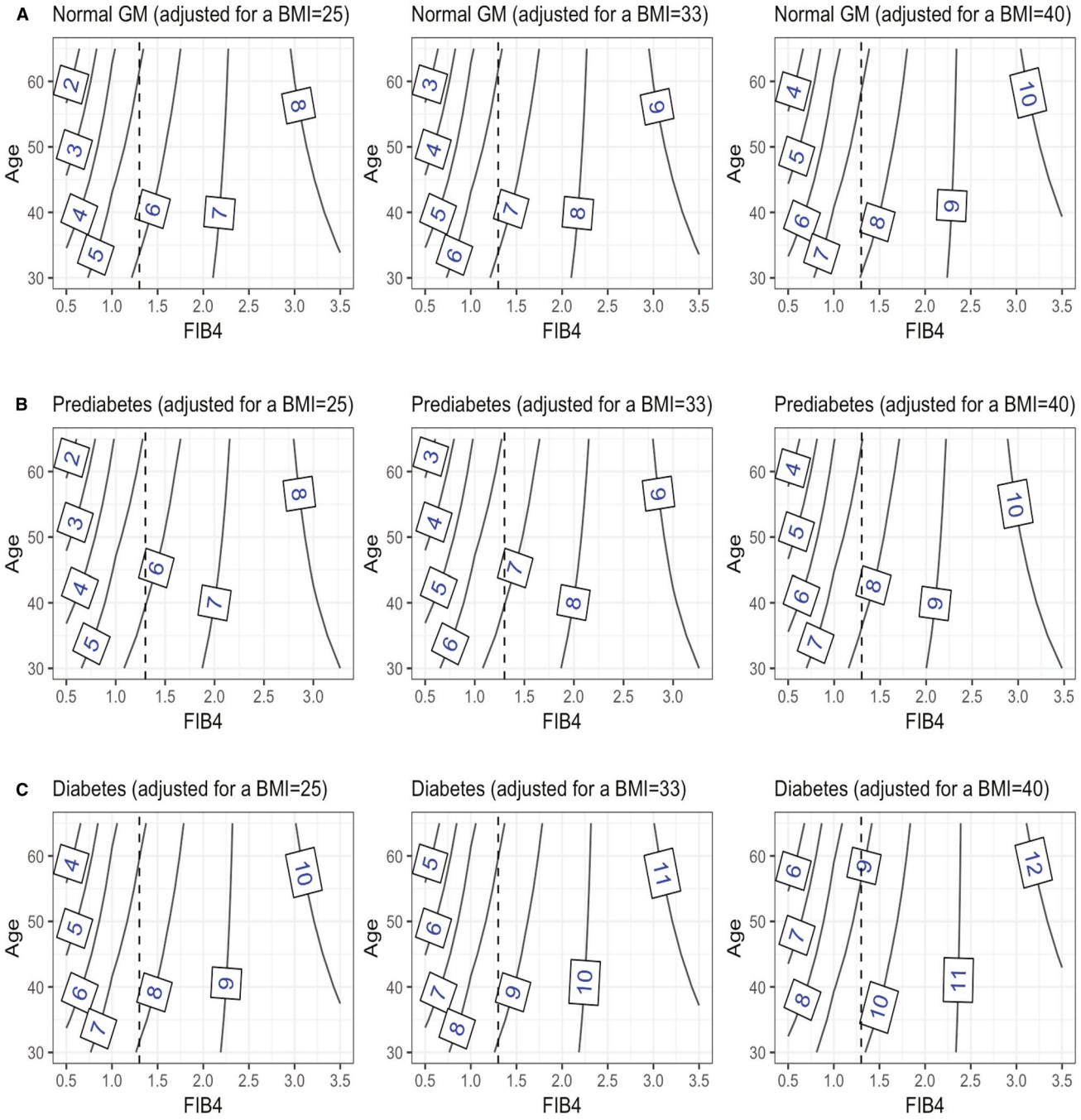

FIG. 5. Predicted mean values of VCTE according to FIB-4 and age (and adjusted for BMI) in patients with normal glucose metabolism (A), prediabetes (B), and diabetes (C). Plots are a graphical display of the linear regression model detailed in the Supporting Information, assessing the association among FIB-4, age, BMI, and glucose metabolism and liver stiffness values (in kilopascals). The lines within the plots show the mean predicted values of liver stiffness as assessed by VCTE. The dashed line represents the 1.3 FIB-4 threshold. Plots are shown for representative BMIs of 25, 33, and 40. Note that at low FIB-4 values, increased age was associated with lower predicted values of VCTE, whereas at high FIB-4 values, increased age was associated with higher predicted VCTE values. Abbreviation: GM, glucose metabolism.

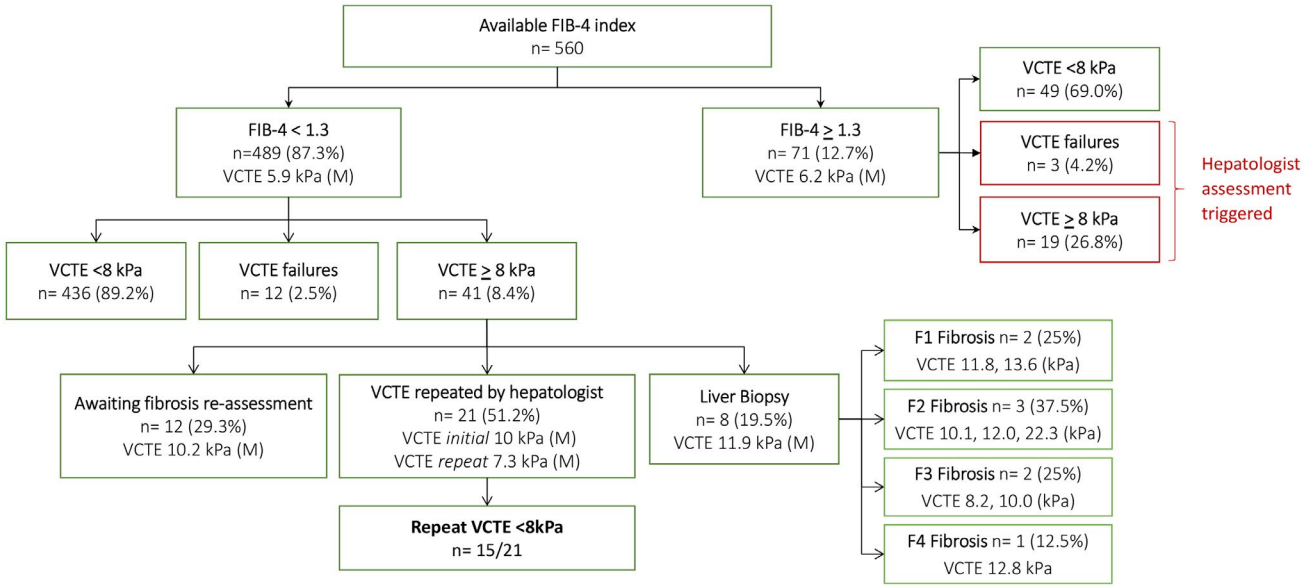

FIG. 6. Impact of the proposed two-stage risk stratification model on the study sample.

TABLE 2. EFFECT OF MODIFYING THE MEAN AGE OF THE SAMPLE IN THE PROPORTION OF PATIENTS WHO WOULD BE TRIAGED AS LOW-RISK BASED ON FIB-4 < 1.3

	Mean Age	Proportion of Patients With a FIB-4 < 1.3
Original sample (n = 560)	40	87% (95% CI: 84-90)
Original sample + 5 years added to every patient	45	82% (95% CI: 78-85)
Original sample + 10 years added to every patient	50	76% (95% CI: 72-79)
Selecting patients with age >43 (n = 223)	51	76% (95% CI: 70-81)

(1.54) strongly supports this notion. The mean age of the patients in our study was also lower (41 versus 51). Because age is a component of FIB-4, it would be expected that more patients in our study would have a FIB-4 of less than 1.3. When we selected a sample of patients over 43 years old (mean age of 51, similar to the McPherson study), 77% of patients were still classified as low-risk, indicating that indeed the population of patients referred to our clinic had earlier disease than those reported in studies in which the patients were selected on the basis of a liver biopsy. In a very recent report in a primary care setting, in a sample with a mean age of 54, 70% of patients had a FIB-4 of less than 1.3,[11] which is consistent with our results.

Previous studies suggested that FIB-4 may underpredict fibrosis in the young, and overpredict fibrosis in older patients.[20,25] Because in our study we did not have liver biopsy data, we explored this issue by modeling the association among FIB-4, age, and VCTE (as a proxy for fibrosis), adjusted by BMI and presence of prediabetes/diabetes (Fig. 4).[21] The effect of age was different in low or high FIB-4 values (reflecting a statistical interaction). This indicates that the weight given to age in the FIB-4 calculation is likely too high in the context of NAFLD. Indeed, FIB-4 was developed in a sample of patients with hepatitis C and human immunodeficiency virus co-infection.[26] Because time from infection is a major determinant of fibrosis in hepatitis C, this might result in an overestimation of the importance of age in a setting such as NAFLD, in which the onset of the disease and the rate of progression is much less well determined.

As additional modifying factors, we show here that higher BMI and the presence of diabetes were associated with higher values of VCTE for a given FIB-4. This might raise the question of whether the proposed FIB-4 threshold (1.3) is still appropriate in obese patients with diabetes. As shown in Fig. 4 and Supporting Fig. S1, the risk of a high VCTE is mostly flat below a FIB-4 of 1.3. This suggests that lower thresholds that would result in the selection of

a much higher number of patients for further specialized assessment, would not be useful. In addition, our modeling suggests that even in extreme cases, such as a 30-year-old patient with diabetes and a BMI of 40, the mean predicted VCTE for a FIB-4 of 1.3 would be 10 kPa (Fig. 4), a value still associated with a relatively low risk of advanced fibrosis in NAFLD.[24]

In our study, only 41 of 489 patients had a VCTE of 8 kPa or higher, despite being stratified as low-risk with a FIB-4 of less than 1.3. In over a third of these patients, repeat VCTE was less than 8 kPa, which might reflect a regression to the mean phenomenon, rapid disease improvement after lifestyle changes, or interoperator variability. The remaining patients were not systematically evaluated with a liver biopsy; therefore, the true proportion of potentially missed advanced fibrosis remains unknown. It is important to note that no triage system can completely eliminate the number of false negatives, and our indirect measurement with VCTE suggests that this risk is extremely low when applied to patients with low pretest probability of advanced fibrosis, such as those referred from primary care. Nevertheless, we have implemented a continuous monitoring system in our program (through administrative records) that will signal the development of liver events in patients triaged as low-risk by the referral system. Due to the predicted low rate of events, this program will require extended follow-up to yield informative results.

Our data showed a VCTE failure rate of 2.7%, much lower than the initial studies validating VCTE for use in NAFLD, which showed failure rates of 23%[6] and 27%.[27] This difference can be explained by the availability of the XL probe in our study. Other studies using both M and XL probes show much lower failure rates of 6.4%-6.7%[23,28] and similar to our findings of 3.2%.[29] Further differences in our failure rate could be associated with the use of different criteria to evaluate unreliability. The aforementioned studies defined unreliability as IQR/median greater than 30%, whereas we only considered VCTE readings as unreliable if the IQR/median was greater than 30% and the VCTE reading was less than 7.1 kPa.[19]

Finally, our program was not designed for systematic screening or case finding, but a pilot program to manage referrals for suspected NAFLD on the basis of abnormal transaminases or incidental finding of fatty liver. Only a small proportion of patients had normal transaminases. Whether the performance of FIB-4-based risk stratification would be the same if applied in the context of screening or case finding programs (that are currently not recommended), in which a substantially greater proportion of patients would have normal transaminases, would need specific evaluation.

In summary, in patients referred from primary care for the evaluation of NAFLD, a two-stage fibrosis risk-stratification model using "FIB-4 First" followed by VCTE demonstrated a significant reduction in the number of patients requiring VCTE and the number of patients requiring hepatology assessment. By allowing movement of the initial risk stratification to the primary care level, this model could be associated with cost benefit to the health care system and to patients who would not be required to travel to major centers for low-risk fibrosis assessment. Indeed, this could prove to be particularly useful in settings with large catchment areas and sparse population density such as ours. A FIB-4 index of 1.3 was an acceptable threshold with low risk for missing advanced fibrosis (as assessed by VCTE). These data provide evidence of the effectiveness of staged assessment of fibrosis and can help in risk stratification and treatment prioritization for lifestyle-based therapies and when medications for NAFLD are approved for use.

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